DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
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RE: Qualified Health Claim Petition: Eggs with enhanced omega-3 fatty acid content and a balanced 1:1 ratio of omega-3/omega-6 fatty acids and reduced risk of heart disease and sudden fatal heart attack. Docket No. 2004Q-0072.

Dear Mr. Steele:

This letter responds to the qualified health claim petition dated January 8, 2004, submitted to the Food and Drug Administration (FDA or the agency), on behalf of Belovo, Inc., pursuant to Sections 403(r)(4) or 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §§ 343(r)(4) and 343(r)(5)(D)). The petition requested that the agency permit a qualified health claim characterizing the relationship between the consumption of Belovo, Inc. omega-3 polyunsaturated fatty acid (PUFA)-enriched eggs (Belovo PUFA-enriched eggs) and a reduced risk of heart disease and sudden fatal heart attack. This petition proposed as a model qualified health claim for eggs:

> Consumption of one egg per day containing 660 mg of omega-3 fatty acids with a balanced ratio of omega-3 to omega-6 fatty acids (1:1) may reduce the risk of heart disease and sudden, fatal heart attack. FDA has determined that the scientific evidence is supportive, but not conclusive, for this claim. See nutrition information for cholesterol content.

FDA filed the petition on February 20, 2004 as a qualified health claim petition and posted the petition on the FDA website for a 60-day comment period, in accordance with the agency's guidance on interim procedures for qualified health claims.[1]

The agency received a letter from a consumer organization about nutrient content claims and health claims for the omega-3 fatty acids EPA and DHA. Because Belovo PUFA-enriched eggs contain approximately twice the amount of EPA and DHA found in a regular egg, FDA placed a copy of the consumer organization's letter in the docket for this qualified health claim petition and is considering it as a comment. The letter states that there is increasing scientific evidence

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[1] Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements: Guidance for Industry and FDA. Rockville (MD): U.S. Food and Drug Administration; July 10, 2003. Available from: http://www.cfsan.fda.gov/~dms/nuttf-e.html

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that EPA and DHA, but not other omega-3 fatty acids, provide cardiovascular benefits, although it does not cite references to support this view. The letter urges FDA to promptly authorize nutrient content claims for foods that are significant sources of EPA and DHA.[2] This comment is relevant insofar as it addresses the issue of qualified health claims in general, but it does not discuss Belovo PUFA-enriched eggs or the Belovo qualified health claim petition specifically, nor does it provide data useful in evaluating that petition.

This letter sets forth the basis for FDA's determination that there is no credible scientific evidence to support the proposed qualified health claim and the reasons the Agency is denying the petition for a qualified health claim with respect to consumption of Belovo, Inc. PUFA-enriched eggs and reduced risk of heart disease and sudden fatal heart attack.

I. Overview of Scientific Evaluation of Data

In a review of a qualified health claim, the agency first identifies the substance and disease or health-related condition that are the subject of the proposed claim and the population to which the claim is targeted.[3] FDA considers the data and information provided in the petition, in addition to other data and information available to the agency that may assist in its review of the relationship between the substance and the disease or health-related condition.[4]

Second, the agency eliminates studies and other information that are not useful to its review of the proposed health claim because they do not pertain to the relationship that is the subject of the claim (e.g., the study tested a different substance or evaluated risk reduction for a disease other than the one in the proposed claim). The agency then separates reports of individual human studies from other types of data and information. FDA focuses its review primarily on reports of human intervention and observational studies because such studies provide the most useful evidence about the proposed health claim.

In addition to reports of individual human studies, the agency also considers other types of data and information in its review, such as meta-analyses[5], review articles[6], and animal and *in vitro*

[2] The letter also urges FDA to authorize only health claims that are supported by "significant scientific agreement" and to abandon consideration of qualified health claim petitions. With respect to the general issue of qualified health claims, FDA continues to follow the recommendations of the July 10, 2003 report of the FDA Task Force on Consumer Health Information for Better Nutrition (http://www.cfsan.fda.gov/~dms/nuttftoc.html); i.e., the agency continues to review qualified health claim petitions in accordance with the guidance on interim procedures for qualified health claims, pending the outcome of the proceeding begun by FDA's advance notice of proposed rulemaking requesting comments on alternatives for regulating qualified health claims, among other topics (68 FR 66040; November 25, 2003).

[3] Interim Evidence-based Ranking System for Scientific Data. Rockville (MD): U.S. Food and Drug Administration; July 10, 2003. Available from: http://www.cfsan.fda.gov/~dms/hclmgui4.html

[4] For brevity, "disease" will be used as shorthand for "disease or health-related condition" in the rest of the section.

[5] A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

studies. These other types of data and information may be useful to assist the agency in understanding the scientific issues about the substance, the disease or health-related condition, or both, but cannot themselves establish a health claim relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine their usefulness regarding factors such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Therefore, FDA uses meta-analyses, review articles, and similar publications[7] to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship. If additional studies are identified, the agency evaluates them individually.

FDA uses animal and *in vitro* studies as background information regarding mechanisms that might be involved in any relationship between the substance and the disease. FDA considers animal and *in vitro* studies in its review when such studies may provide evidence that is useful for evaluating a particular health claim. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes such as digestion, absorption, distribution, and metabolism that affect how humans respond to the consumption of foods and dietary substances.[8] Animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot establish a relationship between the substance and the disease in the absence of appropriate human studies.

FDA screens the reports of individual human studies for flaws and eliminates those with flaws so serious that they render the study results meaningless. Examples of such fatal flaws include lack of a control group and lack of any statistical analysis of the data (Spilker et al., 1991; Federal Judicial Center, 2000).[9,10] Furthermore, for studies in a diseased population to be considered useful in a health claim review for the general U.S. population or target subgroup, evidence is needed to demonstrate that (1) the mechanism(s) for the mitigation or treatment effects measured

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[6] Review articles summarize the findings of individual studies.

[7] Other examples include book chapters, abstracts, letters to the editor, and committee reports.

[8] Institute of Medicine of the National Academies. Dietary Supplements: A Framework for Evaluating Safety. Chapter 7, Categories of Scientific Evidence – In Vitro Data. Washington (DC): The National Academies Press; 2004.

[9] Spilker, B. Guide to Clinical Trials. New York: Raven Press; 1991. pages 59 – 64 and 498.

[10] David H. Kaye & David A. Freedman. Reference Guide on Statistics. In: Federal Judicial Center. *Reference Manual on Scientific Evidence*. 2d ed. 2000. Available from: http://www.fjc.gov

in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations and (2) that the substance affects these mechanisms in the same way in both diseased people and healthy people.

Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and, if so, then determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

In evaluating the proposed qualified health claim for Belovo PUFA-enriched eggs, FDA did not proceed beyond the initial steps in its scientific review because, as discussed below in section II, none of the reports of human studies submitted with the petition were useful to FDA's review. The studies were not useful either because the study tested a substance that was substantially different in PUFA composition than the Belovo egg or because the study was fundamentally flawed in design, conduct, and/or data analysis. As explained above, data and information other than full reports of human studies (such as the abstracts, animal studies, and other items from the petition that are listed at the beginning of section II) may be useful to FDA's review for background, to generate hypotheses, or to explore a substance's possible mechanism of action, but such data cannot establish a substance-disease relationship in humans.

A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of food (21 CFR 101.14(a)(2)). The petition identifies an omega-3 PUFA-enriched egg, produced by Belovo SA (Belgium)-developed technology for feeding chickens, as the substance that is the subject of the proposed claim. The petition notes that the Belovo PUFA-enriched egg is currently being marketed under the name Christopher® egg in the U.S. and under the name Columbus® egg in Europe. According to the petition, these eggs have a PUFA composition consisting of (1) equal amounts of omega-3 and omega-6 polyunsaturated fatty acids (i.e., 1:1 balanced ratio), (2) total omega-3 PUFA content of 660 mg per 50 g egg, and (3) omega-3 PUFA content distributed as 83% alpha-linolenic acid (550 mg/50 g egg) and 17% long-chain omega-3 PUFA (110 mg/50 g egg). The relative proportion of the long chain omega-3 PUFA in the enriched egg is 1:2:8 for eicosapentaenoic acid (EPA, C20:5, n-3), docosapentaenoic acid (DPA, C22:5, n-3) and docosahexaenoic acid (DHA, C22:6, n-3)), respectively. The Belovo PUFA-enriched egg is a specific food and as such is a "substance" as defined by 21 CFR 101.14(a)(2). Therefore, the agency concludes that the Belovo PUFA-enriched egg meets the definition of substance in the health claim regulation (21 CFR 101.14(a)(2)).

The most significant difference between a Belovo PUFA-enriched egg and a regular egg is the Belovo egg's increased content of alpha-linolenic acid (ALA), an 18-carbon omega-3 PUFA. Data provided with the petition (Attachment C: Christopher Egg Analysis) for fat composition analyses of representative Christopher egg and control egg samples indicate the total fat content of the Belovo PUFA-enriched egg is not different from that of a control egg, whereas there is an

approximate 50 percent increase in PUFA content with offsetting decreases in saturated fat and monounsaturated fat content.

The petition asserts that a typical Belovo PUFA-enriched egg contains 175 ± 25 mg cholesterol and that this amount of cholesterol is over 10-20% less cholesterol than that of a standard egg containing about 220 mg cholesterol. These assertions are inconsistent with analytical data submitted in the petition (Attachment C: Christopher Egg Analysis). The petition included cholesterol content data from two Belovo Christopher® PUFA-enriched frozen liquid egg yolk samples (1290 and 1220 mg cholesterol/100g) and from one sample identified as control frozen liquid egg yolk (i.e., frozen liquid egg yolk from standard eggs) (1290 mg cholesterol/100g). Using 17 g as an average weight of the yolk in a large egg, these data translate into cholesterol levels of 207 - 219 mg cholesterol/egg for the Belovo PUFA-enriched egg samples, and 219 mg cholesterol/egg for the control sample analyzed by the petitioner. The petition also included composition data for one Columbus® whole egg composite sample (3.90 mg cholesterol/g). There were no corresponding control whole egg composition data. The USDA Nutrient Data Base for Standard Reference lists the cholesterol content of eggs as 4.23 mg cholesterol/g. These data translate to 195 mg cholesterol/egg (Belovo Columbus®) and 212 mg cholesterol/egg (USDA) for a 50 g large egg. Thus, the data provided do not support the petitioner's assertion that these eggs consistently have a cholesterol content 10-20% lower than standard eggs. Further, it should be noted that this very limited sample size is insufficient to confirm typical cholesterol content of Belovo PUFA-enriched eggs.

The PUFA enrichment of the Belovo PUFA-enriched egg is accounted for entirely by increased content of omega-3 PUFAs; the omega-6 PUFA content is decreased slightly. Within the Belovo egg omega-3 PUFA fraction there is a greater than 20-fold increase in ALA content, and an approximate 2-fold increase in long chain omega-3 PUFAs (i.e., sum of EPA, DPA, and DHA). ALA comprises about 80 percent of the omega-3 PUFA content of the Belovo PUFA-enriched egg.

ALA and the long chain omega-3 PUFAs serve different metabolic functions which are not interchangeable. The metabolic role of EPA is as the precursor for formation of hormone-like substances (e.g., prostaglandins and leukotrienes) which are involved in a large number of cellular functions.[11] DHA is thought to be important for brain development and functioning.[12] The only known metabolic function of ALA is as a precursor for EPA and DHA.[13] However, the rate of ALA to EPA/DHA conversion in humans occurs slowly and the extent to which the conversion occurs in humans is unclear.[14,15] Therefore, although supplementing the diet with

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[11] Jones PJH, Papamandjaris AA. Lipids: Cellular Metabolism. In: Bowman BA, Russell RM, editors. Present Knowledge in Nutrition 8th Edition. Washington (DC): ILSI Press; 2001.

[12] *id.*

[13] *id.*

[14] Emken E. Alpha-linolenic acid conversion to n-3 LC-PUFAs. PUFA Newsletter [on the Internet] 2003 Sep. Available from: http://www.fatsoflife.com/articlePrint.asp?id=130

ALA may result in some increase in tissue levels of long chain omega-3 PUFA, the amount of long chain omega-3 PUFA increase will not be proportional to the amount of supplemental ALA, nor can the amount of increase be predicted.[16] Conversely, long chain omega-3 PUFAs cannot be converted to ALA.[17] Thus, supplementing the diet with omega-3 long chain PUFAs (i.e., EPA and DHA) will not lead to increased tissue levels of ALA.

B. Disease or Health-Related Condition

A disease or health-related condition means damage to an organ, part, or system of the body such that it does not function properly, or a state of health leading to such dysfunction (21 CFR 101.14(a)(5)). The petition is not entirely consistent in identifying the disease or health-related condition that is the subject of the proposed claim. The model health claim proposed in the petition is for "heart disease and sudden fatal heart attack," but the petition's discussion of the prevalence of the disease in the U.S. population refers to "cardiovascular disease," while its discussion of public health benefit anticipated from the proposed claim refers to "coronary heart disease" (CHD). Both heart disease and cardiovascular disease are general terms that encompass a number of different diseases; some forms of heart disease are not cardiovascular diseases, and vice versa. CHD is a more specific term that refers to disease of the arteries supplying blood to the heart; it is both a form of heart disease and a form of cardiovascular disease. Taking into consideration all the information in the petition, including the model qualified health claim, the discussions of disease prevalence and public health benefit, and the studies cited in support of the proposed qualified health claim, FDA concludes that coronary heart disease (CHD) is the specific disease intended as the subject of this claim.

The agency also concludes that coronary heart disease (CHD) is a disease and therefore that the petitioner has satisfied the requirement in 21 CFR 101.14(a)(5). A sudden fatal heart attack is a manifestation of coronary heart disease rather than a separate disease or health-related condition. Myocardial infarction (i.e., heart attack), both fatal and non-fatal, is a CHD endpoint used by FDA in its evaluation of evidence for health claims about reducing the risk of CHD. A substance that reduces the risk of CHD in general would thereby reduce the risk of sudden fatal heart attack; therefore, FDA evaluated the data for both parts of the proposed qualified health claim together.

C. Safety Review

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[15] Wang C, et al. (Tuft-New England Medical Center Evidence-based Practice Center). Effects of Omega-3 Fatty Acids on Cardiovascular Disease. Evidence Report/Technology Assessment No. 94. Rockville (MD): Agency for Healthcare Research and Quality; 2004 March. AHRQ Publication No. 04-E009-2. Contract No.: 290-02-002.

[16] *id.*

[17] Jones PJH, Papamandjaris AA. Lipids: Cellular Metabolism. In: Bowman BA, Russell RM, editors. Present Knowledge in Nutrition 8th Edition. Washington (DC): ILSI Press; 2001.

Under 21 CFR 101.14(b)(3)(ii), if the substance that is the subject of the claim is to be consumed at other than decreased dietary levels, the substance must be a food or a food ingredient or a component of a food ingredient whose use at levels necessary to justify a claim must be demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under applicable food safety provisions of the Federal Food, Drug and Cosmetic Act. The petition asserts that the omega-3 and omega-6 PUFAs with which Belovo PUFA-enriched eggs are enriched are food components of natural biological origin commonly present in food prior to January 1, 1958 and, as such, their use in food is generally recognized as safe (GRAS) through experience based on common use in food.

The Belovo PUFA-enriched egg differs from traditional eggs by a substantial increase in ALA omega-3 PUFA content. The adequate intake (AI) level for ALA established by the Institute of Medicine in its Macronutrient Dietary Reference Intakes Report[18] is 1.1 g/day (adult females) and 1.6 g/day (adult males) based on the highest median intake of ALA by adults in the U.S., where a deficiency is basically nonexistent in free-living populations. The upper boundary of the Acceptable Macronutrient Distribution Range (AMDR) for ALA established by the Institute of Medicine is 1.2 percent of energy. The upper boundary was not set on the basis of a safety concern; rather, it represents the highest level of ALA consumed in the form of foods by adults in the U.S. The AMDR upper boundary is equivalent to 2.7 g ALA/2000 kcal. The daily intake of ALA resulting from adding one Belovo PUFA-enriched egg (0.55 g ALA) to the AI for ALA (based on highest median adult intake) is less than the AMDR upper boundary (1.6 + 0.55 g/day = 2.15 g/day).

The Belovo PUFA-enriched egg has an approximately 2-fold enrichment in the long-chain omega-3 PUFAs of fish oils, compared to conventional eggs. GRAS notifications that FDA has received for uses of fish oils as dietary sources of long chain omega-3 PUFA are based on an assertion that the maximum acceptable daily intake (ADI) for EPA and DHA combined is 3 g per day.[19] FDA has not objected to the basis for self-determinations of GRAS status for these fish oils as food ingredients under conditions of use not expected to contribute to daily intake of EPA and DHA exceeding 3 g.

Although the information about the omega-3 fatty acid enriched egg submitted with the petition and otherwise available to the FDA does not raise concerns that would lead the Agency to question the petitioner's assertion that the levels of omega-3 fatty acids contained in the egg as cited in the petition are safe and lawful, the Agency did not assess whether the petitioner met its

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[18] Institute of Medicine of the National Academies. Dietary Fats: Total Fat and Fatty Acids. In: Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington (DC): The National Academies Press; 2002. p. 8-1 – 8-99.

[19] GRAS Notice Numbers GRN000137, GRN000109, GRN000105, GRN000102, and GRN000097. A summary of all GRAS Notifications received by FDA is available at http://www.cfsan.fda.gov/~rdb/opa-gras.html

burden on this issue. It was not necessary for FDA to do so because the Agency is denying the proposed claims for lack of credible evidence, as discussed in section III below.

II. The Agency's Consideration of a Qualified Health Claim

The petition submitted 74 publications as evidence to substantiate the relationship for this claim. These publications consisted of 18 intervention studies,[20] 28 observational studies,[21] 11 review articles,[22] 2 position papers from the American Heart Association,[23] 2 editorials,[24] 2 meta-analysis articles,[25] 2 food composition surveys,[26] 1 Federal Register notice,[27] 2 food composition data on eggs,[28] 1 book chapter,[29] 3 *in vitro* studies,[30] 3 experimental animal studies,[31] and 1 meeting report.[32]

FDA has identified the following endpoints to use in identifying CHD risk reduction for purposes of a health claim evaluation: coronary events (e.g., fatal and non-fatal myocardial infarction (MI), ischemia (inadequate blood flow caused by blockage of circulation), cardiovascular death (i.e., death from cardiovascular disease), atherosclerosis (narrowing of the arteries), high blood pressure, and serum total and LDL cholesterol. High blood pressure, serum

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[20] Petition's reference numbers: 13-15, 27, 55-63, and 65-69. Citations listed in Appendix A.

[21] Petition's reference numbers: 6, 8, 9, 23, 26-28, 30-37, 39-49, 53, and 54. Citations listed in Appendix B.

[22] Petition's reference numbers: 1, 2, 5, 7, 11, 17, 19, 20, 72, and 74. Citations listed in Appendix C.

[23] Petition's reference numbers: 4 and 16. Citations listed in Appendix D.

[24] Petition's reference numbers: 29 and 38. Citations listed in Appendix E.

[25] Petition's reference numbers: 10 and 12. Citations listed in Appendix F.

[26] Petition's reference numbers: 21 and 22. Citations listed in Appendix G.

[27] Notice of Availability of Proposed Food Guide Pyramid Daily Food Intake Patterns and Technical Support Data and Announcement of Public Comment Period, 68 Fed. Reg. 53536, 2003 Sept 11, 2003.

[28] Human Nutrition Information Service. USDA. Agriculture Handbook No. 8. 1989 Supplement; and USDA National Nutrient Database for Standard Reference, Release 16 (2003 Jul).

[29] Bang HO, Dyerberg J. Lipid metabolism and ischemic heart disease in Greenland Eskimos. In: Draper HH, editor. Advances in nutritional research, Volume 3. New York: Plenum Press; 1980. p. 1-22.

[30] Petition's reference numbers: 24, 25, and 50. Citations listed in Appendix H.

[31] Petition's reference numbers: 50, 51, and 52. Citations listed in Appendix I.

[32] Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. JAMA. 2002;288:2569-78.

total cholesterol, and serum LDL-cholesterol are surrogate endpoints for CHD.[33] A low HDL-cholesterol level is a risk factor for CHD.[34] Atherosclerosis is the underlying cause of CHD, which can lead to the signs of CHD, including coronary events (MI, ischemia) and cardiovascular death.[35] To evaluate whether there is credible evidence that a substance reduces the risk of CHD, FDA considers whether studies using the substance show a beneficial effect on one of these endpoints, which are predictors or indicators of CHD, or a direct effect on the prevalence of CHD.

The agency did not consider all the publications cited in the petition to be useful to its review of this substance/disease relationship. In particular, FDA did not consider the food composition surveys as pertinent because they did not investigate the relationship of the specific PUFA composition of the Belovo PUFA-enriched egg and incidence of heart disease or surrogate measures of CHD risk. Other types of publications that FDA uses only as background are discussed above in section I, Overview of Scientific Evaluation of Data.

A. Assessment of Intervention Studies

Your petition cites a total of 18 intervention studies in support of the proposed qualified health claim.

PUFA Dietary Supplement Intervention Trials

Among the clinical intervention trial reports submitted in the petition were seven studies in which the active treatment was a fish oil supplement at doses ranging from 1.8 g/day to 6 g/day of fish oil omega-3 long chain PUFA (Reis et al., 1989; Kaul et al., 1992; Leaf et al., 1994; Sacks et al., 1995; Singh et al., 1997; von Shacky et al., 1999; and Andrioli et al., 1999). These studies do not provide credible evidence for the proposed claim because the PUFA composition of fish oil is unlike that of the Belovo PUFA-enriched egg. According to the petition, the Belovo PUFA-enriched egg has a 1:1 ratio of omega-3 to omega-6 PUFA, whereas fish oils typically have an omega-3 to omega-6 PUFA ratio of greater than 6:1. The Belovo PUFA-enriched egg also has a 5-fold excess of ALA relative to long chain omega-3 PUFA, whereas fish oil omega-3 PUFA is essentially all long chain PUFA with only an insignificant ALA content. Furthermore, the doses of omega-3 long chain PUFA in the fish oil supplements are all in excess of 10-fold greater than the 0.1 g of omega-3 long chain PUFA provided by one Belovo egg, which is the daily consumption recommendation in the proposed claim. The petition includes no dose-

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[33] National Heart, Blood and Lung Institute (NHLBI); National Institutes of Health. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III); NIH Publication No. 01-3670; 2001. Available from: http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3xsum.pdf

[34] *id.*

[35] National Heart, Blood and Lung Institute (NHLBI); National Institutes of Health. Coronary Heart Disease Explained. Available from: http://nhlbisupport.com/chd1/chdexp.htm

response evidence for omega-3 long chain PUFA to suggest that any effects found with 1.8 to 6 g/day could be extrapolated to the amount of omega-3 long chain PUFA found in Belovo eggs. Because the PUFA composition of the fish oil supplements bears no similarity to that of the Belovo PUFA-enriched egg, and because the daily dose of omega-3 long-chain PUFA in these fish oil studies greatly exceeds the daily intake from a Belovo egg, FDA did not consider the results from the fish oil intervention studies in evaluating the proposed qualified health claim.

The petition cites three reports from the GISSI-Prevenzione trial (Marchioli, et al., 1999; Stone, et al., 2000; and Marchioli, et al., 2002). The dietary intervention in the GISSI-Prevenzione trial was a daily 1 g PUFA supplement containing 0.875 g omega-3 long chain PUFA (as EPA and DHA) without significant amounts of either ALA or omega-6 PUFA. This dietary supplement bears no similarity to the PUFA composition of the Belovo PUFA-enriched egg in which the omega-3 PUFA is predominantly ALA and in which the omega-6 PUFA and omega-3 PUFA content are equal. Therefore, FDA did not consider the results from the GISSI-Prevenzione trial in evaluating the proposed qualified health claim.

In addition to the fish oil supplement group noted above, the clinical intervention trial reported in Singh et al., 1997, included an intervention group that received a daily dietary supplement of mustard oil providing 2.9 g per day of ALA. In this study there were no statistically significant effects of mustard oil on the heart disease risk endpoints evaluated by the investigators (sudden cardiac death, total cardiac deaths, nonfatal MI, and total cardiac events); however, there were statistically significant risk reductions for several MI recovery complications (angina pectoris, arrhythmia, and poor left ventricular function) among the MI patients receiving mustard oil supplements relative to MI patients receiving a placebo. The report provides no information about the mustard oil used other than that it was a refined oil with an ALA content of 14.5 percent. According to the USDA Nutrient Database, mustard oil has an ALA content of about 6 percent.[36] Accordingly, the mustard oil supplement used in Singh et al., 1997 appears to be of atypical, possibly unique composition. Given the report's lack of detailed information about the mustard oil used in the Singh et al., 1997 study, it is impossible to determine whether its PUFA composition was comparable to that of the Belovo egg. Therefore, the relevance of these results to the Belovo PUFA-enriched egg cannot be determined because of a lack of information about the composition of the mustard oil supplement.

The clinical intervention trial reported in Leng et al., 1998 involved use of a PUFA dietary supplement providing 1.68 g per day of omega-6 gamma-linolenic acid (GLA) and 0.27 g per day of EPA. This dietary supplement is fundamentally different in PUFA composition from the Belovo PUFA-enriched egg in that the dietary supplement contains no ALA, and its omega-3 to omega-6 PUFA ratio is only 0.16:1 rather than the 1:1 ratio of the Belovo egg. Further, the Belovo egg contains no GLA, which is the predominant PUFA in the dietary supplement. Therefore, because the PUFA composition of the dietary supplement in this study is

[36] USDA Nutrient Data Laboratory. USDA National Nutrient Database for Standard Reference, Release 17. 2004. Available from: Http://www.nal.usda.gov/fnic/foodcomp

fundamentally different from that of the Belovo PUFA-enriched egg, FDA did not consider the results from Leng et al., 1998 in evaluating the proposed qualified health claim.

In addition to the fish oil supplement group noted above, the clinical intervention trial reported in Andrioli et al., 1999, included an intervention group that received a daily dietary supplement of soy lecithin providing 1.5 g per day of omega-6 PUFA and 0.5 g per day of omega-3 ALA. Although the ALA content of this supplement was comparable to the ALA content of a Belovo PUFA-enriched egg, the PUFA composition of soy lecithin differs from that of the Belovo egg in other important respects. Unlike the enriched egg, soy lecithin contains no long chain omega-3 PUFA and the omega-3 to omega-6 PUFA ratio is only 0.33:1. Therefore, because the PUFA composition of the dietary supplement in this study is fundamentally different from that of the Belovo PUFA-enriched egg, FDA did not consider the results from Andrioli et al., 1999 in evaluating the proposed qualified health claim.

In short, in each of the intervention trials discussed above, the composition of the supplement was substantially different from that of a Belovo PUFA-enriched egg. For this reason, FDA did not consider the results from these studies in evaluating the proposed qualified health claim. All of the PUFA dietary supplement clinical intervention trials discussed above, with the exception of Andrioli et al., 1999, were secondary prevention trials; i.e., they were conducted in patients under treatment for cardiovascular disease. Whether any reported effects in patients with cardiovascular disease would be predictive of CHD risk reduction in healthy people has not been addressed in our evaluation.[37]

Diet Modification Intervention Trials

In the intervention trial reported in Turpeinen et al., 1979, which was conducted in institutionalized subjects, subjects in the treatment group were fed a diet in which vegetable oil replaced most of the dairy fat in their usual diet. Dietary parameters that were changed by this diet modification included, among others, a 50% decrease in saturated fat intake, a 40% decrease in cholesterol intake, and a 3.7 g/day increase in average ALA intake. By comparison, addition of one Belovo PUFA-enriched egg per day to the diet adds approximately 1.6 g/day of saturated fat, approximately 200 mg/day of cholesterol, and only 0.56 g/day of ALA. Because the dietary modification evaluated in this study is not comparable to the dietary modification that would result from consuming one Belovo PUFA-enriched egg daily as recommended in the proposed qualified health claim, FDA did not consider the results from Turpeinen et al., 1979 in evaluating the proposed claim.

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[37] Health claims are intended for the general population (i.e., people who do not have the disease specified in the claim) or a designated subgroup (e.g., women of childbearing age). To reduce the substantial amount of resources and time needed to obtain sufficient endpoint observations for statistical significance, clinical intervention trials are frequently conducted in individuals diagnosed with a particular disease. The relevance of effects of an intervention in diseased individuals to the prediction of effects in healthy people on risk of developing the disease must be considered individually for specific substance-disease relationships. See discussion in section III of FDA's letter responding to health claim petition dated June 23, 2003 (Wellness Petition): Omega-3 Fatty Acids and Reduced Risk of Coronary Heart Disease (Sept. 8, 2004). Available from: http://www.cfsan.fda.gov/~dms/ds-ltr38.html.

The intervention trial reported in Burr et al., 1989 (Diet and Reinfarction Trial - DART) involved three diet modification factors: dietary advice on consumption of fish, fat, or fiber. The "fish advice" was to eat fatty fish at least twice per week or alternatively, subjects unable to comply with the fish advice were encouraged to supplement their diets daily with "Maxepa" fish oil capsules. Among the subjects receiving the "fish advice," the average long chain omega-3 PUFA (as EPA) daily consumption was approximately 3.5-fold greater than the amount of omega-3 long chain PUFA contained in one Belovo PUFA-enriched egg. Furthermore, unlike the Belovo PUFA-enriched egg in which ALA is the predominant omega-3 PUFA and in which there is a 1:1 ratio of omega-3 to omega-6 PUFA, fatty fish and the fish oil supplements contain minimal ALA and approximately a 10:1 ratio of omega-3 to omega-6 PUFA. Because the dietary modification evaluated in this study is not comparable to the dietary modification that would result from consuming one Belovo PUFA-enriched egg daily as recommended in the proposed qualified health claim, FDA did not consider the results from Burr et al., 1989 in evaluating the proposed claim.

The intervention trial reported in de Lorgeril et al., 1999 (Lyon Diet Heart Study) compared the effects of a Mediterranean-type diet to those of a prudent Western diet in MI survivors. There were so many significant dietary differences between the two groups (e.g., the Mediterranean-type diet was significantly higher in dietary fiber than the Western diet and significantly lower in calories, total fat, saturated fat, polyunsaturated fat, and cholesterol) that this study provides no useful information about the effects of adding Belovo PUFA-enriched eggs to the diet. Accordingly, FDA did not consider the results from de Lorgeril et al., 1999 in evaluating the proposed qualified health claim.

In summary, FDA did not consider the results of these studies in evaluating the proposed qualified health claim because the dietary modifications tested in these studies were not comparable to the diet changes resulting from addition of one Belovo PUFA-enriched egg to the daily diet.

As was the case with the PUFA dietary supplement intervention trials, the DART and Lyon Diet Heart Studies were both secondary prevention studies conducted in MI patients. Whether any reported effects in MI patients would be predictive of CHD risk reduction in healthy people has not been addressed in our evaluation.

Enriched Egg Intervention Trials

The petition included reports from three clinical trials in which the intervention involved adding omega-3 PUFA enriched eggs to the subjects' diets (Jiang and Sim, 1993; Prado-Martinez et al., *unpublished*; and Watrin et al., *unpublished*).

The study reported in Jiang and Sim, 1993, was a randomized, parallel arm, 18-day trial with two treatment groups. There was no indication of treatment blinding in the study report. Study subjects were encouraged to maintain their habitual diet but avoid excessive consumption of organ meat, fish, and alcohol. There was no indication that diets were monitored during the study, nor did the report discuss diet composition. The intervention consisted of a breakfast,

consumed daily at the study site, which included either two fried omega-3 PUFA enriched eggs or two fried regular eggs. The omega-3 PUFA-enriched eggs used in Jiang and Sim, 1993, were not Belovo eggs but were similar (not identical) in PUFA composition to a Belovo egg. For example, like Belovo eggs, the eggs in the Jiang and Sim study were predominantly enriched with ALA. Neither the group means nor the variation about the means for measured parameters were reported in this study. Pre- and post-test values for six parameters were compared within groups by paired *t*-tests without adjustment of significance levels for multiple comparisons. There were no statistical comparisons made between groups. FDA finds that this study was not conducted in a manner consistent with generally recognized scientific procedures and principles for dietary intervention trials in that there was no apparent control or monitoring of the diets consumed during the trial, and the analysis of the results lacks a statistical comparison of the active treatment and control treatment groups.[38] Therefore, FDA did not consider the results of Jiang and Sim, 1993 in evaluating the proposed qualified health claim.

The study described in the unpublished report of Prado-Martinez et al.[39] was a randomized, non-blinded, parallel arm, 8 week trial with two dietary groups. Study subjects consumed their usual diets during the study and kept dietary records, which were collected weekly. However, other than frequency of egg consumption, no information about dietary composition was reported. One group consumed their usual diet without modification throughout the study period; this group was reported to have a mean egg intake frequency of 0.65 eggs per day. The second group consumed 1 to 2 Belovo Columbus® eggs per day and excluded other eggs from the diet; this group was reported to have a mean egg intake frequency of 1.13 eggs per day. The variation about the mean daily egg intake was not reported. Pre- and post-test values for 17 parameters were compared within groups by paired *t*-tests without adjustment of significance levels for multiple comparisons. There were no between group statistical comparisons. FDA finds that this study was not conducted in a manner consistent with generally recognized scientific procedures and principles for dietary intervention trials in that there was no apparent control of the diets consumed during the trial, and the analyses of the results lack a statistical comparison of the active treatment and control treatment groups.[40] Therefore, FDA did not consider the results of this study in evaluating the proposed qualified health claim.

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[38] Spilker, B. Guide to Clinical Trials. New York: Raven Press; 1991. pages 59 – 64 and 498.; and David H. Kaye & David A. Freedman. Reference Guide on Statistics. In: Federal Judicial Center. *Reference Manual on Scientific Evidence*. 2d ed. 2000. Available from: http://www.fjc.gov

[39] Petition reference number 14. Prado-Martinez C, Moreno MC, Anderson AHN, Matinez RM, Melero CD. Effects of substituting standard eggs for Columbus® eggs in the diet of Spanish postmenopausal female volunteers.

[40] Spilker B. Guide to Clinical Trials. New York: Raven Press; 1991. pages 59 – 64 and 498.; and David H. Kaye & David A. Freedman. Reference Guide on Statistics. In: Federal Judicial Center. *Reference Manual on Scientific Evidence*. 2d ed. 2000. Available from: http://www.fjc.gov

The study described in the unpublished report of Watrin et al.[41] was a non-randomized, non-blinded, single group trial conducted in hypercholesterolemic patients (mean total cholesterol level 263 mg/dL, mean LDL cholesterol 182 mg/dL) of a lipid management clinic for children. Of the 12 children who completed the study, six were taking lipid-lowering medications, which they continued throughout the trial period. All subjects were assigned to add 4 Belovo Columbus® eggs per week to their diets. All subjects continued following a STEP I cholesterol-lowering diet that they had been following prior to enrollment in the study. The Wilcoxon signed rank test was used to compare pre-and post-test paired measurements. FDA finds that this study was not conducted in a manner consistent with generally recognized scientific procedures and principles for dietary intervention trials in that there was no control group, no randomization, and no blinding of treatment assignment.[42] Further, the usefulness of results seen in this population, children with underlying metabolic disorders contributing to hypercholesterolemia, to prediction of heart disease risk in the general healthy US population is questionable. Therefore, FDA did not consider the results from this study in evaluating the proposed qualified health claim.

In summary, FDA concludes that among the 18 clinical intervention trial reports included in the petition, none is useful in evaluating the effects of Belovo PUFA-enriched eggs on heart disease risk.

B. Assessment of Observational Studies

The petition included a total of 28 observational studies as support for this qualified health claim. These consisted of 17 prospective cohort studies, 4 case-control studies, and 7 ecological studies.

Prospective Cohort Studies

The petition summarizes 17 reports from prospective cohort studies. Nine of these reports are from studies that evaluated an association of fish intake and cardiovascular disease risk (Krumhout, et al., 1985; Krumhout, et al., 1995; Morris, et al., 1995; Mann, et al., 1997; Daviglus, et al., 1997; Albert, et al., 1998; Ooman, et al., 2000; Iso, et al., 2001; and Hu, et al., 2002). Another report cited in the petition (Rissanen, et al., 2000) used serum long chain omega-3 PUFA data as a proxy for fish consumption in Finnish men. Because fish consumption contributes to dietary intake of long chain omega-3 PUFA but does not significantly contribute to dietary intake of ALA nor of omega-6 PUFA, FDA did not consider evidence from these studies of associations between fish intake and cardiovascular disease risk in evaluating the proposed qualified health claim for Belovo eggs, in which the predominant omega-3 PUFA is ALA and which contain equal amounts of omega-3 and omega-6 PUFA. Similarly, a report that evaluated

[41] Petition reference number 15. Watrin I, Braseur D, Carpentier YA. Effect of the consumption of ω-3 fatty acid-enriched eggs on the lipid profiles of adolescents with hypercholesterolaemia.

[42] Spilker B. Guide to Clinical Trials. New York: Raven Press; 1991. pages 59 – 64 and 498.; and David H. Kaye & David A. Freedman. Reference Guide on Statistics. In: Federal Judicial Center. *Reference Manual on Scientific Evidence*. 2d ed. 2000. Available from: http://www.fjc.gov

association of nut consumption frequency and CHD endpoints in Physicians' Health Study data (Albert, et al., 2002a) has no relevance to the PUFA composition of the Belovo PUFA-enriched egg. Nuts in general are not a dietary source of ALA; most of the commonly eaten nuts contain little or no omega-3 PUFA. Walnuts, the only commonly eaten nut with an appreciable ALA content, has an omega-3 to omega-6 PUFA ration of only 0.2:1.[43]

Two prospective cohort studies evaluated correlations of egg consumption to serum cholesterol levels and CHD risk (Dawber et al., 1982; Hu et al., 1999a). In that the dietary variable in these studies was egg consumption in general rather than consumption of PUFA-enriched eggs with a composition comparable to that of the Belovo egg, FDA did not consider the results from these two studies in evaluating the proposed qualified health claim.

Four prospective cohort study reports (Dolecek, 1992; Ascherio et al., 1996; Pietinen et al., 1997; and Hu, et al., 1999b) evaluated associations between heart disease risk and various total diet PUFA variables such as linoleic acid intake, ALA intake, long chain omega-3 PUFA intake, ALA/linoleic acid ratio, or total omega-3/omega-6 PUFA ratio. FDA did not consider the evidence for associations between total dietary PUFA intake and heart disease risk in evaluating the proposed qualified health claim because the proposed claim concerns putative effects of a single food of a specified unique PUFA composition. The dietary PUFA variable analyzed in Hu et al., 1999b was the dietary ALA/linoleic acid ratio (ALA and linolenic acid are the predominant dietary omega-3 and omega-6 PUFAs, respectively); the quintile midpoints for ALA/linolenic ratio in this analysis ranged from 0.07:1 to 0.14:1. Therefore, the results of this study are not relevant to predicting potential effects of consuming an ALA-enriched Belovo egg with an omega-3/omega-6 PUFA ratio of 1:1. Pietinen et al., 1997 evaluated the association of major coronary events or coronary death and intake of total PUFA, linolenic acid, ALA, and omega-3 fish fatty acids. The results reported in Pietinen et al., 1997 show no association of ALA intake and either CHD risk or CHD mortality. Accordingly, even if FDA had considered these results, they would not support the proposed claim. The report of Ascherio et al., 1996 concluded that their data support a specific CHD preventative effect of ALA intake, and also that their data support an effect of saturated fat and cholesterol intakes on increasing CHD risk. Even if FDA had considered these results, they do not support a net CHD risk benefit of consuming ALA-enriched eggs that are also a significant dietary source of saturated fat and cholesterol. The study reported by Dolecek et al., 1992 evaluated intake of both ALA and omega-3 long chain PUFA. Although these authors reported a significant trend of decreased CHD mortality and cardiovascular disease incidence when ALA intake was calculated as a percentage of calories, they did not conclude that their results support the hypothesis that all omega-3 PUFA, both ALA and the long chain PUFA, have an effect on CHD risk. Their conclusion was only that the results support the hypothesis that the fatty acids found primarily in fish oils (i.e., EPA and DHA) protect against cardiovascular disease.

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[43] USDA Nutrient Data Laboratory. USDA National Nutrient Database for Standard Reference, Release 17. 2004. Available from: http://www.nal.usda.gov/fnic/foodcomp

Case Control Studies

The petition summarizes reports from 4 case-control studies. All four of these studies evaluated associations of heart disease risk and long chain omega-3 PUFA intake estimated from either fish consumption (Gramenzi et al., 1990; Siscovick, et al., 2000; and Tavani, et al., 2001) or from serum fatty acid content (Albert, et al., 2002b). As explained above, FDA did not consider evidence for associations of long-chain omega-3 PUFA and disease risk in evaluating the proposed qualified health claim because the proposed claim concerns the Belovo PUFA-enriched egg in which the predominant omega-3 PUFA is ALA, not long chain omega-3 PUFAs.

Ecological Studies

The petition summarizes 7 ecological studies of subpopulation groups, such as Greenland Eskimos and Alaskan Native Americans, which have in common a high intake of fish (Bang and Dyerberg, 1980; Hirai, et al., 1980; Kroman, et al., 1980; Kagawa, et al., 1982; Middaugh, 1990; Newman, et al., 1993; and Rodriguez, et al., 1996). The key dietary variable identified in these studies was the long chain omega-3 PUFA content of cold water fish. Because the subject of the petition is an egg enriched predominantly with omega-3 ALA rather than the long chain omega-3 PUFA of fish, FDA did not consider the results from these ecological studies in evaluating the proposed qualified health claim.

III. Strength of the Scientific Evidence

Based on FDA's review of the totality of publicly available scientific evidence, FDA concludes that there is no credible scientific evidence to support a relationship between Belovo omega-3 PUFA enriched eggs and reduced risk of CHD, including sudden fatal heart attack, because the intervention and observational studies submitted with the petition are not useful in evaluating the proposed health claim. Specifically, the test substances in the great majority of these studies did not have a PUFA composition comparable to that of the Belovo PUFA-enriched egg; the remaining studies were fundamentally flawed in design, conduct, and/or data analysis.

IV. Disqualifying Nutrient Levels

Even if there were credible evidence for the proposed claim, Belovo PUFA-enriched eggs would be disqualified from bearing a health claim because of their cholesterol content. Paragraph (e)(3) of 21 CFR 101.14 prohibits the use of health claims on foods that exceed any of the disqualifying nutrient levels identified in 21 C.F.R. 101.14 (a)(4) , unless FDA has made a finding that such a claim will assist consumers in maintaining healthy dietary practices. The disqualifying cholesterol level identified in paragraph (a)(4) is 60 milligrams (mg) per reference amount and per labeled serving. A standard large egg contains 212 mg of cholesterol.[44] The petition states that a Belovo PUFA-enriched egg contains 175 ± 25 mg of cholesterol, although analytical data provided in the petition suggest the typical cholesterol content of a Belovo PUFA-enriched egg is higher, between 195 and 219 mg.

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[44] USDA Nutrient Data Laboratory. USDA National Nutrient Database for Standard Reference, Release 17. 2004. Available from: http://www.nal.usda.gov/fnic/foodcomp

The petition requests that FDA exempt the proposed qualified health claim for Belovo PUFA-enriched eggs from the disqualifying cholesterol level. In support of this request, the petition asks FDA to consider whether emerging science and new understandings of nutritional factors have made the concept of a fixed disqualifying nutrient level outdated and whether other considerations, such as health benefits from overall food composition, should be determinative in health claim decisions. The petition notes that eggs can be enriched with any fat-soluble nutrient by fortifying the diet of laying hens and argues that enforcement of health claim disqualifying limits would prevent egg producers from informing the public about any health benefit improvements in their products and remove health-based incentives for product improvement. The petition cites seven scientific articles, published between 1982 and 2001, concerning the role of dietary cholesterol and/or eggs in CHD risk, to conclude that available evidence has shown either little or no incremental CHD risk associated with consumption of one egg per day.

In evaluating emerging science and the current understanding of the impact of dietary cholesterol on CHD risk, FDA took into account the 2002 Institute of Medicine (IOM) Dietary Reference Intakes report on macronutrients.[45] As noted by the IOM report, the main adverse effect of dietary cholesterol is increased serum LDL-cholesterol, which is known to result in progressively increasing CHD risk with increasing dietary cholesterol. The IOM report further notes that epidemiological studies (such as those cited in the petition as showing no incremental CHD risk associated with consumption of one egg) have limited power to detect effects of the magnitude resulting from one egg per day and thus do not provide a meaningful basis for establishing adverse effects of dietary cholesterol. The IOM report concluded that a body of evidence shows a positive linear association of CHD risk with dietary saturated and *trans* fatty acids and cholesterol, and that even very low intakes of each may increase risk. Therefore, the intake of cholesterol (as well as saturated and *trans* fatty acids) should be minimized while consuming a nutritionally adequate diet. The IOM report specifically noted that reductions in the frequency of intake or serving size of certain foods such as liver and eggs can help reduce the intake of cholesterol.

The IOM report provides an authoritative independent expert opinion, with which FDA agrees, that dietary intake of cholesterol and saturated fat should be minimized due to its positive linear association with CHD risk. A single Belovo PUFA-enriched egg contains approximately two-thirds of the Daily Value for cholesterol. Further, the saturated fat content of eggs (1.6 g saturated fat/egg) is substantially above the criterion in 21 CFR 101.62(c)(2) for a low saturated fat food (< 1 g saturated fat/reference amount). The existing EPA and DHA omega-3 fatty acid and CHD risk reduction qualified health claim for conventional foods provides for use of the claim on foods low in saturated fat and cholesterol and on fish that are "extra lean" as defined in

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[45] Institute of Medicine of the National Academies. "Cholesterol" and "Macronutrients and Healthful Diets." In: Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington, DC: National Academies Press; 2002. p. 9-1 – 9-32 and 11-1 – 11-95.

21 CFR 101.62(e).[46] Given the significant cholesterol and saturated fat content of Belovo eggs and the well-established association between increased intake of these lipids and higher CHD risk, FDA is not convinced that public health considerations would warrant exercising enforcement discretion with respect to the disqualifying level for cholesterol even if there were credible evidence for a relationship between Belovo PUFA-enriched eggs and CHD risk reduction.

V. Agency's Consideration of Disclaimer or Qualifying Language

We considered but rejected use of a disclaimer or qualifying language to accompany the proposed claim. We concluded that neither a disclaimer nor qualifying language would suffice to prevent consumer deception here, where there is no credible evidence to support the claim. Adding a disclaimer, or incorporating qualifying language that effectively characterizes the claim as baseless is not a viable regulatory alternative because neither the disclaimer nor the qualifying language can rectify the false message conveyed by the unsubstantiated claim. *See, e.g., In re Warner-Lambert Co.*, 86 F.T.C. 1398, 1414 (1975), *aff'd*, 562 F.2d 749 (D.C. Cir. 1977) (pro forma statements of no absolute prevention followed by promises of fewer colds did not cure or correct the false message that Listerine will prevent colds); *Novartis Consumer Health, Inc. v. Johnson & Johnson-Merck Consumer Pharms. Co.*, 290 F.3d 578, 598 (3d Cir. 2002) ("We do not believe that a disclaimer can rectify a product name that necessarily conveys a false message to the consumer."). In such a situation, adding a disclaimer or qualifying language does not provide additional information to help consumer understanding but merely contradicts the claim. *Resort Car Rental System, Inc. v. FTC*, 518 F.2d 962, 964 (9th Cir.) (per curiam) (upholding FTC order to excise "Dollar a Day" trade name as deceptive because "by its nature [it] has decisive connotation for which qualifying language would result in contradiction in terms."), *cert denied,* 423 U.S. 827 (1975); *Continental Wax Corp. v. FTC,* 330 F.2d 475, 480 (2d Cir. 1964) (same); *Pasadena Research Labs v. United States,* 169 F.2d 375 (9th Cir. 1948 (discussing "self-contradictory labels"). In the FDA context, courts have repeatedly found such disclaimers ineffective. *See, e.g., United States v. Millpax, Inc.,* 313 F.2d 152, 154 & n.1 (7th Cir. 1963) (disclaimer stating that "no claim is made that the product cures anything, either by the writer or the manufacturer" was ineffective where testimonials in a magazine article promoted the product as a cancer cure); *United States v. Kasz Enters., Inc.,* 855 F. Supp. 534, 543 (D.R.I.) ("The intent and effect of the FDCA in protecting consumers from . . . claims that have not been supported by competent scientific proof cannot be circumvented by linguistic game-playing."), *judgment amended on other grounds*, 862 F. Supp. 717 (1994).

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[46] U.S. Food and Drug Administration. Qualified health claim enforcement discretion letter: Omega-3 Fatty Acids and Reduced Risk of Coronary Heart Disease (Docket No. 2003Q-0401). Sep 8, 2004. Available from: http://www.cfsan.fda.gov/~dms/ds-ltr38.html

VI. Conclusions

Based on FDA's consideration of the scientific evidence submitted with your petition, FDA concludes that there is no credible evidence to support a qualified health claim for Belovo omega-3 PUFA enriched eggs and reduced risk of heart disease and sudden fatal heart attack. Further, Belovo omega-3 PUFA enriched eggs are disqualified from bearing a health claim under 21 C.F.R. 101.14(e)(3), and FDA does not believe that a qualified health claim about these eggs and reduced risk of CHD would assist consumers in maintaining healthy dietary practices, given the amounts of cholesterol and saturated fat found in the eggs. Thus, FDA is denying your petition for a qualified health claim.

Please note that scientific information is subject to change. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support the use of a qualified health claim or that will support significant scientific agreement.

Sincerely,

Michael M. Landa

Michael M. Landa
Deputy Director for Regulatory Affairs
Center for Food Safety
and Applied Nutrition

APPENDIX A
INTERVENTION TRIAL REPORTS CITED IN PETITION

Petition Ref. No. 13. Jiang Z, Sim JS. Consumption of n-3 polyunsaturated fatty acid-enriched eggs and changes in plasma lipids of human subjects. Nutrition. 1993;9:513-8.

Petition Ref. No. 14. Prado-Martinez C, Moreno MC, Anderson AHN, Martinez RM, Melero CD. Effects of substituting Standard eggs for Columbus® eggs in the diet of Spanish postmenopausal female volunteers [unpublished].

Petition Ref. No. 15. Watrin I, Brasseur D, Carpentier YA. Effect of the consumption of ω-3 fatty acid-enriched eggs on the lipid profiles of adolescents with hypercholesterolaemia [unpublished].

Petition Ref. No. 27. Hirai A, Terano T, Tamura Y, Yoshida S. Eicosapentaenoic acid and adult diseases in Japan: epidemiological and clinical aspects. Journal of Internal Medicine. 1989;225(suppl):69-75.

Petition Ref. No. 55. von Shacky C, Angerer P, Kothny W, Theisen K, Mudra H. The effect of dietary ω-3 fatty acids on coronary atherosclerosis, A randomized, double-blind, placebo-controlled trial. Annals of Internal Medicine. 199;130:554-62.

Petition Ref. No. 56. Leng GC, Lee AJ, Fowkes FGR, Jepson RG, Lowe GDO, Skinner ER, Mowat BF. Randomized controlled trial of gamma-linolenic acid and eicosapentaenoic acid in peripheral arterial disease. Clinical Nutrition. 1998;17:265-71.

Petition Ref. No. 57. Burr ML, Gilbert JF, Holliday RM, Elwood PC, Fehily AM, Rogers S, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART). The Lancet. 1989 Sep 30;8666:757-61.

Petition Ref. No. 58. Reis GJ, Boucher TM, Sipperly ME, Silverman DI, McCabe CH, Baim DS, et al. Randomised trial of fish oil for prevention of resenosis after coronary angioplasty. The Lancet. 1989 Jul 22;8656:177-81.

Petition Ref. No. 59. Kaul U, Sanghvi S, Bahl VK, Dev V, Wasir HS. Fish oil supplements for prevention of resenosis after coronary angioplasty. International Journal of Cardiology. 1992;35:87-93.

Petition Ref. No. 60. Leaf A, Jorgensen MB, Jacobs AK, Cote G, Schoenfeld DA, Scheer J, et al. Do fish oils prevent restenosis after coronary angioplasty? Circulation. 1994;90:2248-57.

Petition Ref. No. 61. Marchioli R, Barzi F, Bomba E, Chieffo C, DiGregorio D, DiMascia R, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction. Time-course analysis of the results of the Gruppo Italiano per lo Studia della

Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation. 2002;105:1897-903.

Petition Ref. No. 62. Singh RB, Niaz M, Sharma JP, Kumar R, Rastogi V, Moshiri. Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: The Indian experiment of infarct survival-4. Cardiovascular Drugs and Therapy. 1997;11:485-91.

Petition Ref. No. 63. Andrioli G, Carletto A, Guarini P, Galvani S, Biasi D, Bellavite P, Corrocher R. Differential effects of dietary supplementation with fish oil or soy lecithin on human platelet adhesion. Thrombosis and Hemostasis. 1999;82:1552-7.

Petition Ref. No. 65. Turpeinen O, Karvonen MJ, Pekkarinen M, Miettinen M, Elosuo R, Paavilainen E. Dietary prevention of coronary heart disease: The Finnish mental hospital study. International Journal of Epidemiology. 1979;8:99-118.

Petition Ref. No. 66. Sacks FM, Stone PH, Gibson M, Silverman DI, Rosner B, Pasternak RC, for the HARO Research Group. Controlled trial of fish oil for regression of human coronary atherosclerosis. Journal of the American College of Cardiology. 1995;25:1492-8.

Petition Ref. No. 67. Stone NJ. The Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardio (GISSI)-Prevenzione Trial on fish oil and vitamin E supplementation in myocardial infarction survivors. Current Cardiology Reports. 2000;2:445-51.

Petition Ref. No. 68. deLorgeril M, Salen P, Martin J-L, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factoirs, and the rate of cardiovascular complications after myocardial infarction: Final report of the Lyon Diet Heart Study. Circulation. 1999;99:779-85.

Petition Ref. No. 69. Marchioli R, et al., for the GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. The Lancet. 1999 Aug 7;354:447-55.

APPENDIX B

OBSERVATIONAL TRIAL REPORTS CITED IN PETITION

Petition Ref. No. 6. Dawber TR, Nickerson RJ, Brand FN, Pool J. Eggs, serum cholesterol, and coronary heart disease. American Journal of Clinical Nutrition. 1982;36:617-25.

Petition Ref. No. 8. Gramenzi A, Gentile A, Fasoli M, Negri E, Parazzini F, LaVecchia C. Association between certain foods and risk of acute myocardial infarction in women. British Medical Journal. 1990;300:771-3.

Petition Ref. No. 9. Hu FB, Stampfer MJ, Rimm EB, Manson JE, Ascherio A, Colditz GA, et al. A prospective study of egg consumption and risk of cardiovascular disease in men and women. JAMA. 1999;281:1387-94.

Petition Ref. No. 23. Bang HO, Dyerberg J. Lipid metabolism and ischemic heart disease in Greenland Eskimos. In: Draper HH, editor. Advances in nutritional research, Volume 3. New York: Plenum Press; 1980. p. 1-22.

Petition Ref. No. 26. Kromann N, Green A. Epidemiological studies in the Upernavik District, Greenland. Incidence of some chronic diseases 1950-1974. Acta Medica Scandinavica. 1980;208:401-6.

Petition Ref. No. 27. Hirai A, Terano T, Tamura Y, Yoshida S. Eicosapentaenoic acid and adult diseases in Japan: epidemiological and clinical aspects. Journal of Internal Medicine. 1989;225(suppl):69-75.

Petition Ref. No. 28. Kagawa Y, Nishizawa M, Suzuki M, Miyatake T, Hananoto T, Goto K, et al. Eicosa polyenoic acids of serum lipids of Japanese islanders with low incidence of cardiovascular diseases. Journal of Nutritional Science and Vitaminology. 1982;28:441-53.

Petition Ref. No. 30. Middaugh JP. Cardiovascular deaths among Alaskan natives, 1980-86. American Journal of Public Health. 1990;80:282-5.

Petition Ref. No. 31. Newman WP, Propst MT, Middaugh JP, Rogers DR. Atherosclerosis in Alaska native and non-natives. The Lancet. 1993 Apr 24;341:1056-7.

Petition Ref. No. 32. Rodriguez BL, Sharp DS, Abbott RD, Burchfiel CM, Masaki K, Chyou P-H, et al. Fish intake may limit the increase in risk of coronary heart disease morbidity and mortality among heavy smokers. Circulation. 1996;94:952-6.

Petition Ref. No. 33. Morris MC, Manson JE, Rosner B, Buring JE, Willett WC, Hennekens CH. Fish consumption and cardiovascular disease in the Physicians' Health Study: A prospective study. American Journal of Epidemiology. 1995;142:166-75.

Petition Ref. No. 34. Albert CM, Hennekens CH, O'Donnell CJ, Ajani UA, Carey VJ, Willett WC, et al. Fish consumption and risk of sudden cardiac death. JAMA. 1998;279:23-8.

Petition Ref. No. 35. Mann JI, Appleby PN, Key TJ, Thorogood M. Dietary determinants of ischaemic heart disease in health conscious individuals. Heart. 1997;78:450-5.

Petition Ref. No. 36. Kromhout D, Bosschieter EB, Coulander C deL. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. The New England Journal of Medicine. 1985;312:1205-9.

Petition Ref. No. 37. Kromhout D, Menotti A, Bloemberg B, Aravanis C, Blackburn H, Buzina R, et al. Dietary saturated fat and *trans* fatty acids and cholesterol and 25-year mortality from coronary heart disease: The seven countries study. Preventative Medicine. 1995;24:308-15.

Petition Ref. No. 39. Daviglus ML, Stamler J, Orenica AJ, Dyer AR, Liu K, Greenland P, et al. Fish consumption and the 30-year risk of fatal myocardial infarction. The New England Journal of Medicine, 1997;336:1046-53.

Petition Ref. No. 40. Dolacek TA. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the multiple risk factor intervention trial. Proceedings of the Society of Experimental Biology and Medicine. 1992;200:177-82.

Petition Ref. No. 41. Pietinen P, Ascherio A, Korhonrn P, Hartman AM, Willett WC, Albanes D, Virtamo J. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men. American Journal of Epidemiology. 1997;145:876-87.

Petition Ref. No. 42. Iso H, Rexrode KM, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, et al. Intake of fish and omega-3 fatty acids and risk of stroke in women. JAMA. 2001;285:304-12.

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APPENDIX F

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APPENDIX G

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APPENDIX H

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APPENDIX I

EXPERIMENTAL ANIMAL STUDIES CITED IN PETITION

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